sCTLA-4, CD4+CD25+Foxp3+ regulatory T cells in Behçet's disease patients

Sirs,

T_{reg} cells plays an important role in controlling immune response and eliminating self-reactive T cells (1). According to their CD25 expression level, these cells are described, CD25 expression ($CD25^{high}$), intermediate ($CD25^{int}$), and low ($CD25^{low}$) (2). CD127 expression is high in activated T cells but low in T_{reg} cells (3). Among $CD4^+CD25^+$ cells, they characterised T_{reg} cells as being $CD4^+CD25^+CD127^{low}$ Foxp3 expression is low in this T_{reg} cells because of its promoter interaction with CD127 (4). CTLA-4 have suppressive role on lymphocyte activation and sCTLA-4, an extracellular secreted, membrane-unbound form of the CTLA-4 receptor (5). Low sCTLA-4 levels are found in normal human serum. High levels were reported in patients with autoimmune disease (6).

Twenty-five BD patients 13 in active period uveitis (9), orogenital ulcer (2), arthritis (2) and 20 age-matched healthy control subjects were included in this study. Disease duration of patients in active and remission period 4.39±1.29 and 8.13±2.04 year respectively. Time for staying in remission 19, 9 months (3-80 months).

Therapeutics and dosage in BD: colchicine 1 mg/day, azathioprine 50 mg/day, sulfasalazine 2 g/day, cyclosporine A 100mg/day and prednisolone 6mg/day were used. After taking blood samples, patients with active BD are started to treat with 1mg/kg prednisolone.

Peripheral venous blood was drawn in EDTA tubes. Analytic flow cytometry was carried out using a Coulter EPICS XL-MCL device (Beckman Coulter USA). sCTLA-4 levels were measured using an ELISA method (Bender MedSystems Austria BMS276).

Statistical analysis was performed with (SPSS) 11.0 (SPSS, Inc., Chicago, IL, USA). The Mann-Whitney U and Kruskal-Wallis tests were used; a $p<0.05$ was considered statistically significant.

BD patients (both active and in remission) had significantly higher $CD4^+CD25^+FoxP3^+$ counts than the control group for ($p<0.01$). They also had higher $CD4^+CD25^+CD127^{low}$ T cells ($p<0.05$) according to controls. There was no difference in the $CD4^+CD25^+FoxP3T_{reg}$ cell and $CD4^+CD25^+CD127^{low}$ cell counts between BD patients with active disease and those in remission ($p>0.05$).

Serum levels of sCTLA-4 were, however, significantly higher in patients with BD in remission than in patients with active disease (0.064±0.149 *vs* 0.332±0914 pg/mL, $p<0.05$). No significant differences could be detected in the sCTLA-4 serum levels between the BD patients and the healthy control group (BD patients 0.236±0.120 *vs* healthy controls 0.228±0.079, $p>0.05$).

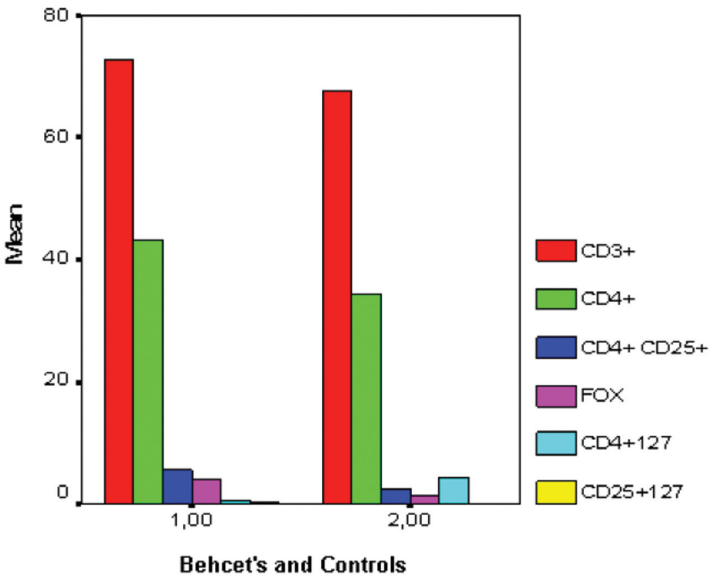

Fig. 1. Lymphocyte counts of Behçet's disease patients and controls.

Several studies have shown a relationship between inflammatory disease and $CD4^+CD25^+T_{reg}$ cells (7). Hamzaoui *et al*. have shown an increase in $CD4^+CD25^+T_{reg}$ cells in active BH. The suppressive function of $CD4^+CD25^{+/high}$ T cells in active BD has been confirmed by the observation (8). sCTLA-4 as an inhibitor molecule and have an important role on T_{reg} function (9). Elevated serum sCTLA-4 levels have been observed in studies performed in different autoimmune diseases. It's relationship to BD could not be found, and the general role and correlations of elevated sCTLA-4 levels could not be elucidated (10, 11). It was reported, in a study of the severity grade of asthma, that the sCTLA-4 levels measured in children with asthma was proportional to acute asthma severity (12). In our study, a substantial increase in the $CD4^+CD25^+Foxp3^+$ cell count of BD patients but the same group of patients showed no change in sCTLA-4 levels. The course of the inflammatory process in BD is chronic and very variable. These results cannot be explained by the particular action in BD of sCTLA-4 as an immune modulator; exposing CTLA-4 presentation in T_{reg} cells should provide a more realistic evaluation. Such an explanation could be based on the loss of T_{reg} cell function achieved through CTLA-4, if one considers that sCTLA levels were different in active BD and in remission. These study results may be seen as supporting the idea of a loss of T_{reg} function in the active disease phase.

It is possible that cellular markers that are expressed or secreted in excessive amounts could lack effectiveness in the periphery. Such in sufficiency in controlling inflammation could represent the cause of the uncontrolled inflammation which appears in the attack period. The need for more advanced functional studies to expose more clearly the inhibitory mechanisms participating to the disease etiopathogenesis is obvious.

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